

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-199

FINAL PRINTED LABELING

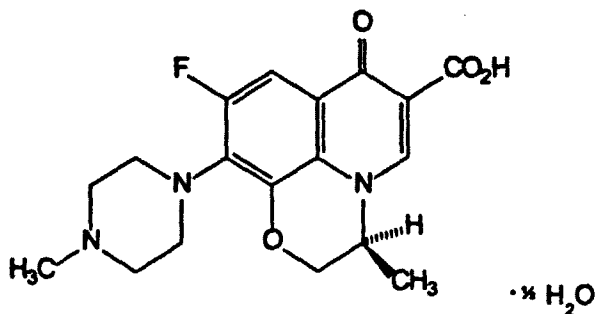
**QUIXIN™
(LEVOFLOXACIN OPHTHALMIC SOLUTION) 0.5%**

*Basis of Approval
Submitted Aug 15, 2000*

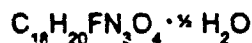
DESCRIPTION

QUIXIN™ (levofloxacin ophthalmic solution) 0.5% is a sterile topical ophthalmic solution. Levofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. Levofloxacin is the pure (-)-(S)-enantiomer of the racemic drug substance, ofloxacin. It is more soluble in water at neutral pH than ofloxacin.

Structural formula



levofloxacin hemihydrate



Mol Wt 370.38

Chemical Name: (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid hemihydrate.

Levofloxacin (hemihydrate) is a yellowish-white crystalline powder.

Each mL of QUIXIN™ contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin.

Contains: **Active:** Levofloxacin 0.5% (5 mg/mL); **Preservative:** benzalkonium chloride 0.005%; **Inactives:** sodium chloride and water. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

QUIXIN™ solution is isotonic and formulated at pH 6.5 with an osmolality of approximately 300 mOsm/kg. Levofloxacin is a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Levofloxacin concentration in plasma was measured in 15 healthy adult volunteers at various time points during a 15-day course of treatment with QUIXIN™ solution. The mean levofloxacin concentration in plasma 1 hour postdose, ranged from 0.86 ng/mL on Day 1 to 2.05 ng/mL on Day 15. The highest maximum mean levofloxacin concentration of 2.25 ng/mL was measured on Day 4 following 2 days of dosing every 2 hours for a total of 8 doses per day. Maximum mean levofloxacin concentrations

increased from 0.94 ng/mL on Day 1 to 2.15 ng/mL on Day 15, which is more than 1,000 times lower than those reported after standard oral doses of levofloxacin.

Levofloxacin concentration in tears was measured in 30 healthy adult volunteers at various time points following instillation of a single drop of QUIXIN™ solution. Mean levofloxacin concentrations in tears ranged from 34.9 to 221.1 µg/mL during the 60-minute period following the single dose. The mean tear concentrations measured 4 and 6 hours postdose were 17.0 and 6.6 µg/mL. The clinical significance of these concentrations is unknown.

Microbiology:

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves the inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair, and recombination.

Levofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms and is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from β-lactam antibiotics and aminoglycosides, and therefore may be active against bacteria resistant to β-lactam antibiotics and aminoglycosides. Additionally, β-lactam antibiotics and aminoglycosides may be active against bacteria resistant to levofloxacin.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10⁻⁹ to 10⁻¹⁰).

Levofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic Gram-positive microorganisms

Corynebacterium species*
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus (Groups C/F)
Streptococcus (Group G)
Viridans group streptococci

Aerobic Gram-negative microorganisms

*Acinetobacter lwoffii**
Haemophilus influenzae
*Serratia marcescens**

*Efficacy for this organism was studied in fewer than 10 infections.

The following *in vitro* data are also available, but their clinical significance in ophthalmic infections is unknown. The safety and effectiveness of levofloxacin in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

These organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Levofloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following ocular pathogens.

Aerobic Gram-positive microorganisms

Enterococcus faecalis
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus pyogenes

Aerobic Gram-negative microorganisms

Acinetobacter anitratus
Acinetobacter baumannii
Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Pseudomonas fluorescens

Clinical Studies:

In randomized, double-masked, multicenter controlled clinical trials where patients were dosed for 5 days, QUIXIN™ demonstrated clinical cures in 79% of patients treated for bacterial conjunctivitis on the final study visit day (day 6 – 10). Microbial outcomes for the same clinical trials demonstrated an eradication rate for presumed pathogens of 90%.

INDICATIONS AND USAGE

QUIXIN™ solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-positive microorganisms

Corynebacterium species*
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus (Groups C/F)
Streptococcus (Group G)
Viridans group streptococci

Aerobic Gram-negative microorganisms

*Acinetobacter lwoffii**
Haemophilus influenzae
*Serratia marcescens**

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS

QUIXIN™ solution is contraindicated in patients with a history of hypersensitivity to levofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR INJECTION.

QUIXIN™ solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemic quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to levofloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS

General:

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for Patients:

Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemic quinolones have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Drug Interactions:

Specific drug interaction studies have not been conducted with QUIXIN™. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration for 2 years; the highest dose (100mg/kg/day) was 875 times the highest recommended human ophthalmic dose.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the *in vivo* mouse sister chromatid exchange assay. It was positive in the *in vitro* chromosomal aberration (CHL cell line) and *in vitro* sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproduction in rats at oral doses as high as 360 mg/kg/day, corresponding to 3,150 times the highest recommended human ophthalmic dose.

Pregnancy: Teratogenic Effects. Pregnancy Category C:

Levofloxacin at oral doses of 810 mg/kg/day in rats, which corresponds to approximately 7,000 times the highest recommended human ophthalmic dose caused decreased fetal body weight and increased fetal mortality.

No teratogenic effect was observed when rabbits were dosed orally as high as 50 mg/kg/day, which corresponds to approximately 400 times the highest recommended maximum human ophthalmic dose, or when dosed intravenously as high as 25 mg/kg/day, corresponding to approximately 200 times the highest recommended human ophthalmic dose.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin is excreted in human milk. Caution should be exercised when QUIXIN™ is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in infants below the age of one year have not been established. Oral administration of quinolones has been shown to cause arthropathy in immature animals. There is no evidence that the ophthalmic administration of levofloxacin has any effect on weight bearing joints.

Geriatric Use:

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most frequently reported adverse events in the overall study population were transient decreased vision, fever, foreign body sensation, headache, transient ocular burning, ocular pain or discomfort, pharyngitis and photophobia. These events occurred in approximately 1-3% of patients. Other reported reactions occurring in less than 1% of patients included allergic reactions, lid edema, ocular dryness, and ocular itching.

DOSAGE AND ADMINISTRATION

Days 1 and 2: Instill one to two drops in the affected eye(s) every 2 hours while awake up to 8 times per day.

Days 3 through 7: Instill one to two drops in the affected eye(s) every 4 hours while awake up to 4 times per day.

HOW SUPPLIED

QUIXIN™ (levofloxacin ophthalmic solution) 0.5% is supplied in a white, low density polyethylene bottle with a controlled dropper tip and a tan, high density polyethylene cap in the following sizes:

2.5 mL - NDC 65086-135-25

5 mL - NDC 65086-135-05

Storage: Store at 15° - 25°C (59° - 77°F).

Rx Only.

Manufactured by:
Santen Oy, P. O. Box 33
FIN-33721 Tampere, Finland

Marketed by:
Santen Inc., Napa, CA 94558, U.S.A.

Licensed from Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan
U.S. PAT. NOS. 4,382,892; 4,551,456; 5,503,407

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